AWARD NUMBER: W81XWH-14-1-0534

TITLE: Frontoparietal priority maps as biomarkers for mTBI

PRINCIPAL INVESTIGATOR: Cheryl A Olman

CONTRACTING ORGANIZATION: University of Minnesota
                                 Minneapolis, MN 55455-2070

REPORT DATE: October 2016

TYPE OF REPORT: Annual (Year 2)

PREPARED FOR: U.S. Army Medical Research and Materiel Command
                Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
Oct 2016	Annual	30 Sep 2015– 29 Sep 2016

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
	W81XWH-14-1-0534
Frontoparietal priority maps as biomarkers for mTBI	**5b. GRANT NUMBER**
	5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)	5d. PROJECT NUMBER
Cheryl A Olman	**5e. TASK NUMBER**
	5f. WORK UNIT NUMBER
E-Mail: caolman@umn.edu	

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)	8. PERFORMING ORGANIZATION REPORT NUMBER
University of Minnesota Office of Sponsored Projects 200 Oak St SE Minneapolis, MN 55455-2009	

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012	
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
This project involves a series of behavioral and magnetic resonance imaging (MRI) experiments that will determine the degree to which difficulties with visual attention, saccade targeting and motion perception associated with mild traumatic brain injury (mTBI) can be attributed to damaged cortical brain networks serving attention and eye movement planning. The hypothesis being tested is that spatial attention and eye movement deficits associated with mTBI result from disruption of the gray matter and/or the white matter in cortical networks that control attention allocation and eye movements. A combination of functional MRI and diffusion-weighted imaging will allow us to measure (1) integrity in cortical networks in frontal and parietal brain regions responsible for attention allocation and eye-movement planning, (2) integrity in the white matter carries outputs from these regions to the sub-cortical nuclei that control eye movements, and (3) correlation between these biomarkers and behavioral measures of visual performance in veterans who have and have not experienced mTBI. No results are available at the time of writing; preliminary data analysis is underway.

15. SUBJECT TERMS
mTBI, fMRI, DTI, psychophysics, vision, convergence insufficiency

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**	Unclassified	8	**19b. TELEPHONE NUMBER** *(include area code)*
Unclassified	Unclassified	Unclassified			

Table of Contents

INTRODUCTION

This project involves a series of behavioral and magnetic resonance imaging (MRI) experiments that will determine the degree to which difficulties with visual attention, saccade targeting and motion perception associated with mild traumatic brain injury (mTBI) can be attributed to damaged cortical brain networks serving attention and eye movement planning. The hypothesis being tested is that spatial attention and eye movement deficits associated with mTBI result from disruption of the gray matter and/or the white matter in cortical networks that control attention allocation and eye movements. A combination of functional MRI and diffusion-weighted imaging will allow us to measure (1) integrity in cortical networks in frontal and parietal brain regions responsible for attention allocation and eye-movement planning, (2) integrity in the white matter that contains the axons that carry the outputs of these cortical computations to the sub-cortical nuclei that actually control eye movements, and (3) correlation between these biomarkers and behavioral measures of visual performance in veterans who have and have not experienced mTBI.

KEYWORDS

mTBI
fMRI
DTI
psychophysics
vision
convergence insufficiency

ACCOMPLISHMENTS

Specific Aim 1: behavioral characterization of convergence insufficiency, tracking in 3D, spatial attention, saccade execution and motion perception		
Major Task 1: human subjects approval	Timeline (months)	Accomplishment
Submit necessary documentation to University of Minnesota IRB	1	Completed 8/8/2014
Respond to stipulations and provide additional doc.	2	Completed 9/22/2014

Local IRB approval	3	Received 10/2/2014
Submit necessary documentation to HRPO	3	Completed 10/2/2014
Milestone Achieved: HRPO Approval	6	Veteran Affairs Medical Center (VAMC) IRB approval received on 5/20/2015. Change in protocol approval received from University of Minnesota IRB on 6/19/2015. HRPO approval received 6/28/2015.
Major Task 2: preparation of task and training of study personnel		
Programming of tasks	1-3	Completed 12/15/2014.
Project coordinator practices running behavioral sessions on other study personnel	3-4	Completed.
Analysis of pilot behavioral data to ensure all necessary tools are in place; make any necessary refinements to task	4-6	Completed 6/30/2015.
Milestone(s) Achieved: behavioral protocol established and rehearsed	6	Completed 6/30/2015.
Major Task 3: behavioral assessments		
Recruitment of subjects on VA Protocol 4581-B.	7-11	Protocol modified August, 2016, to add in-person recruiting for participants engaged in other studies
Scheduling of eligible subjects for behavioral assessments of 85 subjects (30 controls, 55 with TBI)	7-15	35 Subjects have completed the behavioral protocol as of 9/30/2016
Analysis of behavioral data and assignment to Phase II study group on rolling basis	7-15	Analysis of first cohort is beginning.
Milestone Achieved: 48 subjects identified for Phase II of study (48 subjects = 24 controls, 24 with visual complaints)	15	24 participants were identified and scanned during Year 2.
Specific Aim 2: correspondence between behavioral and imaging measures of visuospatial function		
Major Task 4: establish imaging protocol		
Analysis of pilot data acquired on healthy controls in the course of other studies	3-6	Underway.
Phantom studies on 7T scanner to establish QA protocol	7	Completed.
Milestone Achieved: MRI protocol prepared	8	Completd.
Major Task 5: acquire MRI measures, which include DTI and fMRI		
Complete scanning sessions (Visit 2) for 12 participants	9-12	Completed May, 2016..
Preliminary analysis of 12 datasets to verify quality	9-12	Completed June, 2016.
Visit 2 for remaining 36 participants	12-18	12 additional visits completed as of 9/30/2016.
Milestone Achieved: 48 subjects scanned	18	
Major Task 6: analysis and publication		
Analysis of imaging data	12-20	On-going.
Presentation of preliminary findings at Society for Neuroscience or similar conference	18	Preliminary behavioral results presented at annual meeting of Vision Sciences Society in St Pete's Beach, Fl, May, 2016.
Writing and submission of manuscript	20-22	
Milestone Achieved: publication of association between	24	

o **What were the major goals of the project?**

See SOW table above.

o **What was accomplished under these goals?**

Behavioral data collection protocol is proceeding well.

Imaging data acquisition is completed on first cohort. Because behavioral and imaging data indicate a continuous, rather than bimodal, distribution between "TBI" and "control" groups, design is revised and correlational analysis across all participants. This reduces total number of participants required.

Preliminary analyses indicate strong associations between frontal white matter integrity and smooth pursuit eye movements, smooth pursuit eye movements correlate with reading speeds, and reading speeds correlate with parietal cortex white matter integrity.

o **What opportunities for training and professional development has the project provided?**

- Study staff are being trained to analyze DTI, fMRI and eye-tracking data.

o **How were the results disseminated to communities of interest?**

Presentation at vision conference in May, 2016 (see table above).

o **What do you plan to do during the next reporting period to accomplish the goals?**

Plans for upcoming reporting period will adhere to the SOW, above.

IMPACT

For each of the statements below, there is nothing to report because the project remains in preliminary phases. However, brief statements about anticipated impact when the project meets its goals are also included.

o **What was the impact on the development of the principal discipline(s) of the project?**
At completion, impact on principle discipline will be evidence for involvement of the brain's gray and white matter in visual dysfunction following mTBI, and refinement of hypotheses about the specific mechanisms by which brain damage may contribute to visual dysfunction.

o **What was the impact on other disciplines?**
At completion, impact on other disciplines will be improved measures for correlating behavioral and MRI (DTI, fMRI) data.

o **What was the impact on technology transfer?**
At completion, impact on technology transfer will be progress of DTI as a biomarker in the clinical setting.

o **What was the impact on society beyond science and technology?**
At completion, impact on society will be improved understanding of the effects of mTBI on the brain, leading to better policies regarding treatment of TBI.

CHANGES/PROBLEMS

o **Changes in approach and reasons for change**

Study design moved away from group differences because even control participants report experiences that make it likely they experienced some kind of TBI, so all participants are being analyzed on a continuum defined by behavioral measures rather than a group distinction (formerly based on clinical interviews).

o **Actual or anticipated problems or delays and actions or plans to resolve them**

Nothing to report.

- o **Changes that had a significant impact on expenditures**

  Slow progress on recruiting means that we carry a balance to fund future MR experiments, should they be necessary.

- o **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

  Nothing to report.

PRODUCTS

- o **Publications, conference papers, and presentations**

  "Visual Attention and Eye Movement Deficits in Patients with Traumatic Brain Injury", Tori D. Espensen-Sturges, Timothy J. Hendrickson, Andrea N. Grant, Scott R. Sponheim, Cheryl A. Olman. Poster presentation at Vision Sciences Society Annual Meeting, St Pete's Beach, Florida, May 13-17, 2016.

- o **Website(s) or other Internet site(s)**

  Nothing to report.

- o **Technologies or techniques**

  Nothing to report

- o **Inventions, patent applications, and/or licenses**

  Nothing to report.

- o **Other Products**

  Nothing to report.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Cheryl Olman, PI – no change.

Andrea Grant, staff scientist – no change.

Tori Espensen-Sturges, Graduate Research Assistant – added to assist with data analysis after project coordinator left.

Essa Yacoub, consultant – no change.

- o **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Nothing to report.

- o **What other organizations were involved as partners?**

Minneapolis VAMC, overseeing participant recruitment.

SPECIAL REPORTING REQUIREMENTS

Quad Chart attached.

APPENDICES

None.

Frontoparietal priority maps as biomarkers for mTBI

ERMS/Log Number and Task Title: MR130374
Award Number: W81XWH-14-1-0534

PI: Olman **Co-Is**: Sponheim, Jerde   **Org:** University of Minnesota/Minneapolis VA   **Award Amount:** $250,000 / 2 years
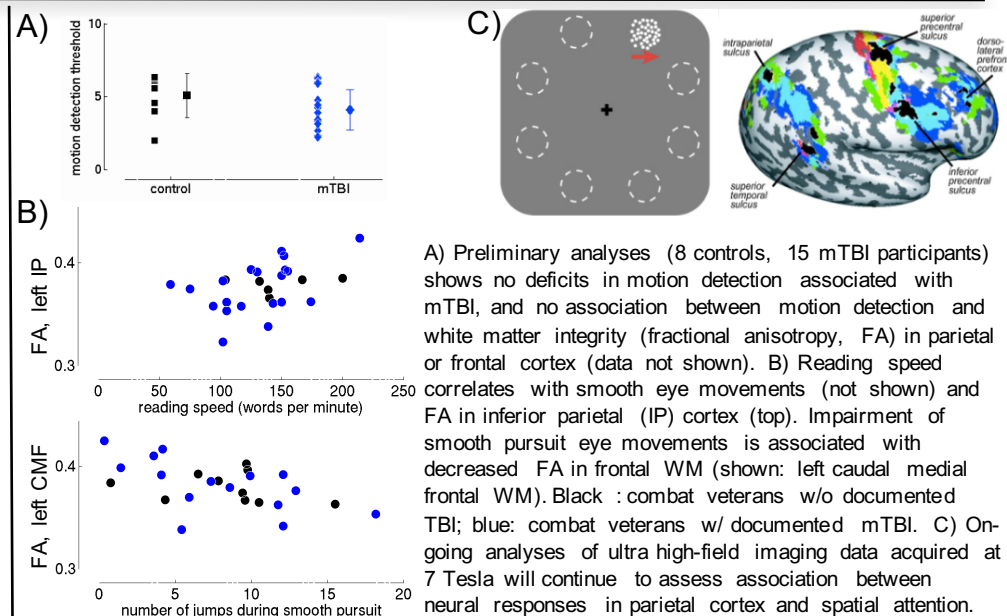
Study/Product Aim(s)

• Hypothesis: visual performance deficits in attention and eye-movements are driven by cortical damage
  • Aim 1: to determine strength of correlation between performance on attention allocation and eye-movement tasks and functional neuroimaging markers of attention regulation
  • Aim 2: to quantify association between white matter integrity and these behaviors.

Approach

In a cohort of 85 subjects who have experienced mTBI and controls, behavioral data will be acquired on the tasks illustrated at right.

DTI data acquired on all participants (as part of previous studies) will be compared against behavioral data to discover predictors of deficits in reading and smooth pursuit eye movements.

A subset will also participate in functional MRI experiments to assess association between visual behaviors and fMRI-measured attention competence.

A) Preliminary analyses (8 controls, 15 mTBI participants) shows no deficits in motion detection associated with mTBI, and no association between motion detection and white matter integrity (fractional anisotropy, FA) in parietal or frontal cortex (data not shown). B) Reading speed correlates with smooth eye movements (not shown) and FA in inferior parietal (IP) cortex (top). Impairment of smooth pursuit eye movements is associated with decreased FA in frontal WM (shown: left caudal medial frontal WM). Black : combat veterans w/o documented TBI; blue: combat veterans w/ documented mTBI. C) On-going analyses of ultra high-field imaging data acquired at 7 Tesla will continue to assess association between neural responses in parietal cortex and spatial attention.

Timeline and Cost

Activities	CY	14	15/16	17
Regulatory compliance				
Beh. data acquisition and analysis				
MRI data collection/analysis				
Final analysis and publication				
Estimated Budget (total $K)		**$25**	**$150**	**$75**

Updated: July 6, 2016 to reflect no-cost extension granted 6/8/2016

Goals/Milestones

CY14 Milestones Completed – Study initiation
☐ Received U of M IRB approval on 10/2/2014; VA IRB approval on 5/20/2015
☐ Received HRPO approval on 6/28/2015
CY15 Milestones Completed – Comparison of different visual behaviors
☐ Conducted initial behavioral and DTI data analysis (see above)
CY16 Goals – Connection of visual behaviors with imaging biomarkers
☐ Complete MRI data acquisition from subset of TBI patients and controls
☐ Increase sample size for results shown above
CY17 Goals (with no-cost extension) – study completion
☐ Publish analysis of behavioral and imaging data

Comments/Challenges/Issues/Concerns
• Combat veterans with and without documented TBI are not showing distinction, in most behavioral and imaging measures; visual deficits exist on a continuum.
• Study design is therefore revised from to rely correlations across population rather than simple group differences.

Projected Annual Budget: annual direct costs $83k

Personnel: 8-10% effort for co-Is:	$20.0k
Project coordinator, consultant, support staff:	$40.0k
Equipment time (MRI) and subject compensation:	$20.0k
Travel to annual meeting; conference travel Y1, pub fees Y2	$ 3.0k